

## REMARKS

### I. Status Summary

Claims 1-27, 46-53, and 61-75 are pending and have been examined.

Claims 74 and 75 have been objected to by the United States Patent and Trademark Office (hereinafter "the Patent Office") on a formal basis.

Claims 8 and 9 have been rejected under 35 U.S.C. § 112, second paragraph.

Claims 1-10, 15, 19-27, 46-53, 64-73, and 75 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc Natl Acad Sci USA* 94:5231-5236 (hereinafter "Diehl"). Claims 1-4 have also been rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy").

Claims 11-14, 16-18, and 63-74 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans"), and further in view of Hedrich (1981) Genetic Monitoring, Volume 1, Chapter 8 (hereinafter "Hedrich"). Claims 1-10, 15, 19-27, 46-53, and 60-75 have also been rejected under this section over the combination of Lipp *et al.* (1999) *J APOA Intl* 82:923-928 (hereinafter "Lipp") in view of U.S. Patent No. 6,573,438 to Mettler et al. (hereinafter "the '438 Patent").

Claims 1, 46, and 74 have been amended. Support for the amendments to claims 1 and 46 can be found throughout the specification as filed, including particularly at page 18, lines 5-8, which provides a definition for "renewable population of genetically diverse individuals". The amendment to claim 74 is limited to correcting a typographical error. Accordingly, no new matter has been added as a result of the claim amendments.

Reconsideration of the application based on the remarks set forth below is respectfully requested.

### II. Response to the Objection to the Claims

Claims 74 and 75 have been objected to because claim 74 includes two steps (b) and no step (a). Applicants would like to thank the Patent Office for pointing out the

typographical error in claim 74. This error has been corrected in the instant amendment, and thus applicants respectfully request that the objection be withdrawn.

III. The Presently Disclosed Subject Matter

The presently disclosed subject matter pertains *inter alia* to methods for identifying a genetic locus that modulates a phenotype (claims 1, 60, 64, and 75, and dependents thereof) and methods for identifying an interaction between a genetic locus and a non-genetic factor, wherein the interaction modulates a phenotype (claims 46 and 74, and dependents thereof). Although the specific steps of the methods differ, all of the methods include the following general steps:

- (1) providing a renewable population of genetically diverse individuals;
- (2) mapping the genomes of the genetically diverse individuals that display the phenotype.

Thus, each of the claimed methods employs renewable populations of genetically diverse individuals. As such, it is desirable for the Patent Office to understand the nature of the renewable population of genetically diverse individuals, as it is only through proper claim term interpretation that this understanding can be gained.

First, the population is a renewable population. This does not simply mean that if, for example, the population were a population of humans, that a new population of humans could be generated. This assertion was made by the Patent Office in a telephone interview dated January 13, 2005, in which the Patent Office asserted that “renewable” reads on standard breeding of individuals. If it were true that “renewable” could be so broadly construed, then the term would have no meaning whatsoever because all populations would be renewable. Clearly, applicants’ use of the term “renewable” in relation to their population evinces an intent to impart on the population a characteristic that is different than that gained from standard breeding.

In fact, it is clear from the examples of how to generate a “renewable” population disclosed in the specification that these populations do indeed differ from populations that arise from standard breeding. The specification discloses that renewable populations can be generated, for example, by crossing different RI lines, by

backcrossing RI lines, by using cloned populations, and by using panels of cell lines. In each case, the common thread that runs through these examples is that the method of generating the renewable population (e.g., crossing or backcrossing RI lines, cloning, and causing cell lines to divide) results in a population for which each individual has a genome that can be exactly duplicated by repeating the generating method. This is further pointed out in the amendments to claims 1 and 46, in which the renewable population is recited as one that can be regenerated.

Thus, it is clear from proper consideration of the specification that in a renewable population, the genomes that exist in the individuals that make up the renewable population can be exactly duplicated. This is clearly the case in cloning and cell division, where each daughter cell has precisely the same genome as its parent cell. In these cases, therefore, a renewable population is generated.

However, during sexual reproduction, new genomes are generated that contain chromosomal contributions from each parent. Thus, for a diploid organism like a human (which has 23 chromosome pairs), breeding of one male and one female can generate  $46^2$  (i.e., over 2000) different chromosomal possibilities in any given child. Thus, and contrary to the Patent Office's assertions, a population that consists of the offspring of a given pair of humans (i.e., the common children of those humans) is not a renewable population because if the same pair of humans were to have additional children, no child would be genetically identical to any other child that existed.

Furthermore, the above simplistic model assumes that recombination does not occur in the gametes of the parents. However, since meiotic recombination occurs on every chromosome in every gamete, at no time when an individual reproduces does he or she pass the exact same genetic information on to his or her offspring. As such, standard breeding of humans can never produce a renewable population of diverse individuals.

In fact, there is only one condition under which breeding can ever result in the production of a renewable population, and that is when each member of the breeding pair is homozygous at every genetic locus. Under these circumstances, each member of a chromosome pair in an individual is identical to the other member of the pair, and

when meiotic recombination occurs, identical pieces of genetic information are exchanged. This results in each chromosome of a chromosome pair having the exact same arrangement of the exact same genetic information after the recombination event as it did before the recombination event. Under these conditions, each offspring receives the same the same genetic information from each parent, and thus the population is renewable. This does not require that each parent be genetically identical to each other, however. Parents can be different from each other genetically provided that individually they are homozygous at every locus.

Turning to the specification of the instant application, the Patent Office's attention is directed to page 18, lines 5-8: "The phrase 'renewable population of genetically diverse individuals' refers to a population that can be faithfully regenerated and comprises a limited repertoire of possible genotypes, although individuals within the population are genetically diverse". A human population does not satisfy this definition because a human population cannot be "faithfully regenerated" for the reasons set forth hereinabove. Thus, a human population, like any other population generated by standard breeding, is not a renewable population.

Turning now to the nature of "genetically diverse", applicants respectfully submit that consistent with the instant specification, genetic diversity is a characteristic of an individual, and does not require consideration of any other genotype in the population. Thus, an animal that is homozygous at every locus, such as a recombinant inbred animal, is not genetically diverse. This was the intent behind amending the relevant claims to include the element "wherein a plurality of the genetically diverse individuals are heterozygous for a detectable polymorphism". This was for clarity only, as this "wherein" clause clarifies what is intended by the phrase "genetically diverse individual".

Applicants further respectfully submit that it is clear upon proper consideration of the specification that the presently disclosed subject matter differs from traditional mapping experiments that employ RI lines. In RI mapping, the genome of every individual that is mapped is homozygous at every locus. The instant specification discloses beginning on page 14, line 30:

The term “genetic noise” or “genetic background” or “residual genotype” as used herein each refer[s] to a level of genetic variation. In a genetic mapping experiment, genetic noise is inversely correlated with genetic diversity. For example, genetic noise is significant in a recombinant inbred population due to the limited number of unique genotypes.

Furthermore, on page 20, beginning on line 16, the instant specification discloses:

A novel aspect of the disclosed mapping approach lies in the features of the mapping population. In contrast to existing populations for genetic mapping, a renewable population of genetically diverse individuals, or a panel of cell lines representing individuals derived from a diverse population, is characterized by minimal genetic noise as well as environmental noise (Figure 2). Recombinant inbred lines are a commonly used mapping population that has substantially low environmental noise, but power of detection is hindered by poor genetic diversity.

(emphasis added). Taking these two passages into consideration, it is clear that the presently disclosed subject matter differs from mapping strategies based on the use of RI lines, and further that RI lines have poor genetic diversity.

With this framework in mind, applicants respectfully submit the following remarks with respect to the Patent Office’s rejections of the pending claims.

#### IV. Response to the Anticipation Rejections

##### IV.A. The Rejection Over Diehl

Claims 1-10, 15, 19-27, 46-53, and 64-75 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl. The Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci (Col2a1, Col1a1, and Col3a1) that modulate a phenotype (facial clefting) in mice. According to the Patent Office, Diehl “performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse” using recombinant inbred (RI) mouse strains provided by M. Nesbitt. Official Action, page 3. The AXB and BXA RI lines are asserted to be crosses between A/J and C57BL6/J strains which were bred by intercrossing RI lines and maintained as a “renewable population of genetically diverse individuals”. Diehl is also asserted to disclose the identification of loci using inbred lines using less than about 100

strains, identifying multiple genetic loci that modulate a phenotype, the modulation of a phenotype by a non-genetic factor (drug exposure), and the identification of an interaction among two or more non-genetic factors and a genetic locus.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Initially, applicants respectfully submit that the Patent Office's assertion on page 6 of the Official Action that "claim 1 is so generically written that a written work of Gregor Mendel and his pea plants would likely be anticipatory" clearly points out that the Patent Office is interpreting the claims in a manner that is inconsistent with the specification. Gregor Mendel worked with normal pea plants to study the segregation of simple monoallelic traits. In no case did Mendel ever produce a renewable population of genetically diverse individuals.

To elaborate, there were seven traits the transmission of which Mendel studied:

1. flower color (purple or white)
2. flower position (axial or terminal)
3. stem length (long or short)
4. seed shape (round or wrinkled)
5. seed color (yellow or green)
6. pod shape (inflated or constricted)
7. pod color (yellow or green)

What Mendel observed is that after crossing the plants, intermediate phenotypes were not observed for any of these traits in any progeny plant – it was always one or the other. Thus, the population may have appeared to be renewable because from an individual cross, purple or white flowers were always generated.

However, and as is pointed out in greater detail hereinabove, the ability of a population to be regenerated is not limited to one locus, but encompasses every locus of every individual. Stated another way, the entire genome (*i.e.*, the genotype at every locus) of every individual of the population must be regenerable for the population to be renewable. This is clearly pointed out in the instant specification, which discloses that a

renewable population is a regenerable population, meaning that the members of the population must be capable of being regenerated (*i.e.*, not simply replaced with other members of the same species). The amendments to claims 1 and 46 further clarify this aspect of the population. This was not the case in Mendel's experiments, and thus Mendel's experiments cannot possibly be interpreted to anticipate claim 1.

Continuing with the instant rejection, applicants respectfully submit that the Patent Office is misconstruing the teachings of Diehl with respect to the establishment and breeding of the RI lines. The Patent Office asserts that the RI lines obtained from Nesbitt were bred by intercrossing RI lines and maintained as a renewable population of genetically diverse individuals. Applicants respectfully submit that this assertion is an inaccurate characterization of the Diehl reference, as the Diehl reference does not state that the RI lines were bred by intercrossing. In fact, applicants respectfully submit that one of ordinary skill in the art knows that RI lines cannot be maintained by intercrossing, because intercrossing RI lines would destroy the homozygosity at every locus that is the hallmark of an RI line.

Rather, applicants respectfully submit that Diehl states the following: "Mice were then bred and maintained in a colony at the University of Michigan" (Diehl at page 5232; emphasis added). As is known in the art, RI lines are maintained by breeding a male and a female from the same line to each other. Thus, in a properly constructed RI line, the male and the female are homozygous at every locus, and in fact are genetically identical to each other. Thus, breeding two genetically identical animals maintains the RI line because the progeny are all genetically identical to each other and to their parents and none are genetically diverse (*i.e.*, heterozygous at any locus) as is defined in the instant specification.

An intercross, on the other hand, involves breeding of two animals that are not genetically identical. Typically, an intercross is between two animals that are each heterozygous for the same marker. Gregor Mendel's pea plant experiments are prototypical examples of intercrosses. In a typical intercross, a male that has, for example, an Aa genotype at one locus is bred to a female that is also Aa at that locus.

The progeny of this mating show the 1:2:1 distribution of AA:Aa:aa genotypes that is typical of a heterozygous cross.

In the instant application, an intercross is exemplified by breeding RI individuals from different RI lines (*i.e.*, animals that are not genetically identical). This is disclosed on pages 6, 8, and 18 of the instant specification, which disclose crossing  $n$  recombinant inbred lines to generate a renewable population of genetically diverse individuals comprising  $n(n-1)$  different RIX lines, representing all possible reciprocal pair wise combinations of recombinant inbred lines. As can be understood from the specification, breeding  $n$  different RI lines to produce  $n(n-1)$  different RIX lines involves breeding each of the  $n$  lines to every other line except to itself. Thus, the specification discloses employing RI lines in every possible breeding arrangement except the one that can be used to maintain the RI line itself.

Reference is also made to Figure 1, which clearly demonstrates that non-recombinant individuals can be used to create  $n$  recombinant inbred (RI) individuals, which can then be crossed to recombinant inbred individuals of another RI line to produce  $n(n-1)$  recombinant, genetically diverse, and regenerable individuals. This breeding strategy excludes breeding an individual of a specific RI line to another individual of the same RI line, since that would not introduce heterozygosity in the offspring and thus would not introduce genetic diversity into the offspring. Reference is further made to Figure 2, which shows that F2 (F1 intercross) and RIX (RI intercross) individuals have excellent genetic diversity, while RI individuals do not. Applicants respectfully submit that the difference between the former and the latter is that the latter are homozygous at every locus, whereas the former are each heterozygous for at least one (although typically many more) locus.

Thus, the Patent Office's assertion that the RI lines were maintained by intercrossing finds no support in Diehl, is contrary to the method that one of ordinary skill in the art would employ to maintain an RI line, and as such is inaccurate.

Furthermore, and also contrary to the Patent Office's assertions, applicants respectfully submit that Diehl does not disclose any breeding strategy that produces genetically diverse individuals. As recited in claims 1, 46, 74, 75, and dependents



thereof, a genetically diverse individual is an individual that is heterozygous for a detectable polymorphism. While it is unclear exactly how the Patent Office is defining “genetically diverse”, applicants respectfully submit that it is clear that the Patent Office’s definition is not consistent with the specification, and thus cannot be employed in interpreting the claims. Since in Diehl no RI mouse is heterozygous at any loci, no mice disclosed in Diehl are genetically diverse. The Official Action simply states that Diehl discloses genetically diverse individuals without describing one single mouse that is in fact genetically diverse. Applicants respectfully submit that in fact, it is not possible for the Patent Office to point to any disclosure in Diehl that provides support for this contention.

In response, the Patent Office asserts that applicants are attempting to incorporate limitations from the specification into the claims. However, applicants respectfully submit that the Patent Office is not appreciating that there is a difference between “interpreting claim terms in light of the specification” and “reading limitations from the specification into the claims”. The former cannot properly be viewed as imposing a limitation on the claims since it is axiomatic that claim interpretation begins with consideration of the specification. As such, interpreting a claim in a manner that is consistent with the specification can never “limit” a claim term because the claim term necessarily encompasses the full scope that one of ordinary skill in the art would understand the specification to impart to that claim term.

The Patent Office, on the other hand, is interpreting various claim elements inconsistently with the specification, and then asserting that applicants’ interpretation, which is consistent with the specification, amounts to importing limitations from the specification into the claims. Clearly, this is an improper approach to claim interpretation. Stated another way, the Patent Office’s approach of giving the claim terms their “broadest reasonable interpretation” is being pursued without taking into account the teachings of the specification, leading the Patent Office to assert that applicants’ purportedly narrower interpretation amounts to importing limitations from the specification. However, even assuming *arguendo* that applicants’ proffered interpretations are narrower than the Patent Office’s, applicants’ interpretations are fully

consistent with the specification, whereas the Patent Office's interpretations are not. The Patent Office's approach is thus unreasonably broad in that it conflicts with the specification, and as such is not in compliance with the requirements of the In re Morris, In re Prater, and In re Zletz decisions cited by the Patent Office on page 6 of the Official Action.

Accordingly, applicants respectfully submit that when the phrases employed in the claims are interpreted in a manner that is consistent with the overall teachings of the specification, it is clear that the Diehl reference does not support the instant rejection under 35 U.S.C. § 102(b).

To elaborate, applicants respectfully submit that Diehl at best discloses a straight-forward mapping experiment based on RI lines. Thus, every breeding arrangement disclosed in Diehl involved breeding a male mouse to a genetically identical female mouse. Accordingly, every single mouse disclosed in Diehl is homozygous at every locus.

This is in contrast to the instant claims. Independent claims 1, 46, 60, 64, 74, and 75 either explicitly or implicitly recite performing the mapping step on individuals that are heterozygous for a detectable polymorphism. None of the individuals produced by Diehl are heterozygous at any locus, and as such, cannot be understood to anticipate this element of the claims. Applicants respectfully submit that the specification as a whole clearly informs one of ordinary skill in the art that the genomes of the individuals that are mapped are not homozygous, and as such, it is clear that Diehl does not anticipate the subject matter of any of the independent claims.

Accordingly, applicants respectfully submit that claims 1, 46, 60, 74, and 75 have been distinguished over Diehl, as each of these independent claims explicitly recite that a plurality of the genetically diverse individuals are heterozygous for a detectable polymorphism. Claims 2-10, 15, 19-27, and 47-53 all depend directly or indirectly from distinguished claims 1 and 46, and thus these claims are also believed to be distinguished from Diehl.

Turning now to the subject matter of claims 64 and dependents thereof, claim 64 recites providing a renewable population of genetically diverse individuals comprising a

panel of cell lines. Diehl clearly does not teach mapping using cell lines, and thus cannot be read to anticipate claim 64. Claims 65-73 all depend directly or indirectly from distinguished claim 64, and thus these claims are also believed to be distinguished from Diehl.

Therefore, applicants respectfully submit that the rejection of claims 1-10, 15, 19-27, 46-53, 64-73, and 75 under 35 U.S.C. § 102(b) over Diehl has been addressed. Applicants respectfully request that the rejection be withdrawn, and the claims allowed at this time.

#### IV.B. The Rejection Over Bellamy

Claims 1-4 have been rejected under 35 US § 102(b) upon the contention that the claims are anticipated by Bellamy. According to the Patent Office, Bellamy teaches a method for identifying a genetic locus that modulates a phenotype comprising (a) providing a renewable population of diploid humans that are genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Further, Bellamy is asserted to teach the above method wherein the renewable population comprises a panel of cell lines derived from the genetically diverse individuals.

After considering the rejection and the Patent Office's basis for the rejection, applicants respectfully traverse the rejection and submit the following.

Initially, applicants respectfully submit that the Patent Office again misconstrues the meanings of several claim terms in an effort to force the Bellamy reference to support the rejection of claims 1-4. The terms at issue in this instance are "phenotype" and "mapping". Applicants have maintained that a "phenotype" is a characteristic of an individual, and does not require reference to the rest of the population. In fact, the Patent Office's proffered definition of phenotype emphasizes that a phenotype is a visible characteristic or trait of an organism. Band sharing is not a visible characteristic of an organism because it is only "visible" when a population is considered. Thus, applicants respectfully submit that the Patent Office's reliance on the definition of "phenotype" found on the UC biotech's website does not support the instant rejection,

but rather supports applicants' position that band sharing is not a phenotype. Moreover, applicants respectfully submit that the DNA fingerprinting disclosed in Bellamy is at best a form of genotyping, not phenotyping.

Nonetheless, even assuming *arguendo* that band sharing were a phenotype, applicants respectfully submit that claim 1 of the instant application recites in step (c) that a genetic locus is identified that modulates the phenotype. Band sharing is not modulated by any locus, and thus Bellamy cannot possibly be read to disclose this element of claim 1. The Patent Office has provided no evidence that any locus modulates band sharing. In fact, since band sharing is a passive consequence of genotype, no locus can be interpreted to modulate it. Since the term "modulate" clearly envisions an active role of a locus on a phenotype (see specification at page 17, which states "The term 'modulate' in the context of a phenotype, refers to the action of a genetic or non-genetic factor to contribute to the phenotype" (emphasis added)), no locus modulates band sharing, and the Patent Office's assertions to the contrary represent an attempt by the Patent Office to impose on the claims a definition of "modulate" that is inconsistent with the specification.

Furthermore, applicants respectfully submit that step (b) of claim 1 recites mapping the genomes of the individuals. The Patent Office asserts that "genetic mapping" is the "determination of the relative locations of genetic information on chromosomes". The Patent Office then asserts that "the placement and size range of band sharing for first degree relatives in the Gaza family for example, meets the limitation of mapping the genome" (see Official Action at page 8). Applicants respectfully submit that the latter assertion is completely inconsistent with the definition offered by the Patent Office, and thus does not support the instant rejection.

For example, the Patent Office does not state how the placement and size range of band sharing is a mapping technique. In fact, applicants respectfully submit that no loci are mapped in Bellamy at all, as the bands are identified by hybridizing multi-locus probes to total genomic DNA. Since multi-locus probes by definition bind to multiple sites in the genome, they cannot be used for mapping purposes because they do not uniquely identify any single chromosome. In other words, since genetic mapping is

designed to give an approximation of how far a locus is from a known marker position on a chromosome (e.g., in centimorgans, frequency of recombination, etc.), multi-locus probes cannot be used for mapping because they are not positioned at a single known location. Rather, single copy probes/markers are typically employed for genetic mapping, and Bellamy does not use single copy probes/markers.

And finally, applicants respectfully submit that the Patent Office's assertion that "determination of the relative locations of genetic information on chromosomes" is "a generic and non-limiting phrase" indicates the definition chosen by the Patent Office is inappropriate for analyzing the instant claims. As stated hereinabove, it is the Patent Office that asserts that "genetic mapping" is the "determination of the relative locations of genetic information on chromosomes". Applicants respectfully submit that given that the term "mapping" must be understood in the context of the specification from the perspective of the skilled artisan, and that one of ordinary skill in the art understands the metes and bounds of "mapping", the definition chosen by the Patent Office is only "generic and non-limiting" when the understanding of one of ordinary skill in the art is not taken into account.

Applicants respectfully submit that on the one hand the Patent Office attempts to employ this definition to support the instant rejection over Bellamy, and then asserts that the definition is useless for analyzing the claims. Applicants' agree that the definition "determination of relative locations of genetic information on chromosomes" is uninformative when considered in isolation, but that when the skilled artisan's knowledge is brought to bear, that it is clear that "determination of relative locations" clearly refers to identifying where on a chromosome a specific locus is placed relative to some other known locus.

To elaborate, scientific publications that discuss genetic mapping typically disclose that one locus is mapped relative to an identifying position (*i.e.*, a second locus, or in mouse, the centromere, which is located at the end of the chromosome in this species), and a distance between the two is presented that contains a region of the genome modulating the phenotype under study. Generally, this distance is in megabases, kilobases, centimorgans, as an expression of recombination frequency

between the loci, etc. An example of this is seen in Table 2 of Diehl, which discloses regions associated with clefting susceptibility. As disclosed therein, Table 2 of Diehl lists 16 chromosomal regions as being associated with clefting susceptibility, and each one is disclosed as being within some distance in centimorgans (cM) from a given centromere.

Thus, mapping is understood by the skilled artisan to include more than just finding that a multi-locus probe can be used to identify bands of different sizes and/or that a multi-locus probe hybridizes to some random, unidentified sequence on a random, unidentified segment of an unidentified chromosome, which applicants respectfully submit that is what is disclosed in Bellamy. Instead, mapping requires that a specific locus be identified at a specific position on a specific chromosome at a specific distance from a known position, which delineates a genomic interval modulating a phenotype. Applicants respectfully submit that Bellamy does not teach this, and indeed, that the multi-locus probes of Bellamy cannot be used to accomplish this.

And finally, applicants respectfully submit that “mapping” is specifically defined in the specification, and thus the Patent Office’s reliance on extrinsic evidence (*i.e.*, the UC website definition) is improper. Applicants respectfully direct the Patent Office’s attention to page 14 of the specification, which recites in part:

The term “mapping”, “genetic mapping”, “mapping of the genome”, or “genotyping” each refer[s] to a method for describing a position of a genetic locus in terms of recombination frequency with a genetic polymorphism. The results of a mapping method are described in map units or Morgans.

Specification at page 14, lines 5-8. Thus, applicants respectfully submit that the use of the term “mapping” is consistent with a description of a distance between two loci, and is not consistent with a description of band sharing. Given that each band that is identified by the multi-locus probes results from the hybridization of one or more copies of one, two, three, or four of the multi-locus probes to an unknown sequence present on that band, applicants respectfully submit that it is not possible based on Bellamy to assign any of the probes to any of the bands, nor is it possible to generate any information as to the relative positions or distances between any loci on any band.

Accordingly, applicants respectfully submit that Bellamy does not teach genomic mapping of a genetic locus that modulates a phenotype. As a result, Bellamy cannot be read to anticipate the method of claim 1. Applicants further respectfully submit that claims 2-4 all depend from claim 1, and thus are also believed to be distinguished from Bellamy. Therefore, applicants respectfully request that the rejection of claims 1-4 over under 35 U.S.C. § 102(b) over Bellamy be withdrawn, and that the claims be allowed at this time.

V. Responses to the Obviousness Rejections

V.A. Response to the Rejection over Diehl in view of  
Dindzans and Hedrich

Claims 11-14, 16-18, and 63-73 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans, and further in view of Hedrich. The asserted teachings of the Diehl reference are presented hereinabove. According to the Patent Office, the Diehl reference does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines or that the genetically diverse individuals will be a natural by product from the use of multiple parent strains. This deficiency is asserted to be cured by Dindzans, which the Patent Office contends teaches that multiple parents are necessary for the breeding of mice in an attempt to map genes and in the elucidation of mechanisms of genetic control. The Patent Office further asserts that Dindzans does not teach the derivation of RI lines from at least 3, 4, or 8 non-recombinant parent lines, but that Hedrich teaches the organization of breeding colonies from a founding colony made up of 8-10 breeding pairs. From this, the Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the identification of a genetic locus that modulates a phenotype method Diehl so as to have included the diverse population of non-recombinant parent lines of Dindzans and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich for the expected benefit that more parents would obviously result in a more diverse progeny, but also from the expected benefit of providing an additional means for furthered variation among mouse

lines and for the ability taught be Hedrich of making “it possible to select among the lines that one which matches the original standards best”.

After careful consideration of the rejection and the Patent Office’s bases therefore, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully wish to comment on certain erroneous assertions that have been made by the Patent Office in support of the instant rejection. First, the Patent Office appears to assert that genetically diverse individuals will be a natural by product from the use of multiple parent strains. This assertion is based on an interpretation of “genetically diverse” that is not consistent with the specification. Genetic diversity is not equivalent to having genetic information that can be traced back to multiple different parental strains. This difference is exemplified by RI lines. Whether a member of an RI line can trace its genetic information back to 2, 3, 4, 8, or more original non-recombinant parental lines is irrelevant because an RI individual is by definition not genetically diverse since it is not heterozygous at any locus. Therefore, a genetically diverse individual is not necessarily a natural by product from the use of multiple parent strains if the multiple parent strains have been used to create RI lines or other inbred lines, which are then maintained by brother/sister matings. In this case, all progeny are genetically identical to each other and to their immediate parents. These individuals are not genetically diverse.

Furthermore, Dindzans does not teach using a diverse population of non-recombinant parent lines. Instead, Dindzans, like Diehl employed only the A/J and C57BL6/J non-recombinant parent lines, neither of which was genetically diverse because each of which was inbred (*i.e.*, was intentionally bred to be homozygous at every locus). Accordingly, inbred lines, whether non-recombinant inbred lines or recombinant inbred lines are never genetically diverse.

Additionally, the assertion that “more parents would obviously result in more diverse progeny” clearly shows that the Patent Office is employing the term “diverse” in a manner that this inconsistent with the specification. Since individuals can only have two parents, it is clear that the reference to “more parents” is intended to encompass



both first order parents and higher order “parents”. Consistent with the instant specification, applicants respectfully submit that even the use of 8 different non-recombinant inbred lines does not necessarily introduce genetic diversity into an individual if that individual has been bred to homozygosity. Therefore, “more parents would obviously result in more diverse progeny” is indicative of the Patent Office’s overly broad interpretation of the term “diverse”.

Turning now to the rejection itself, the Patent Office maintains that Dindzans employs multiple progenitors for the expected benefit that using multiple progenitors creates “a unique assortment of parental genes” that is “useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control”. Applicants respectfully submit that this teaching is irrelevant to the instant claims. In fact, since both Diehl and Dindzans teach basic, straightforward mapping experiments based on recombinant inbred strains in which no individuals are genetically diverse as defined in the instant specification, Dindzans does not teach one of ordinary skill in the art anything in addition to what is already disclosed explicitly or implicitly in Diehl. In both references, multiple recombinant inbred lines are analyzed because that is the way that RI mapping is performed.

Accordingly, applicants respectfully submit that Dindzans does nothing to cure the deficiencies of Diehl discussed hereinabove. For example, Dindzans does not teach or suggest employing a renewable population of genetically diverse individuals, wherein the individuals are heterozygous for a detectable polymorphism. This is clearly pointed out in the Dindzans reference itself, which on page 2355 states that “each RI strain consists of a unique assortment of parental genes that are homozygous at every locus”, and that “such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control” (emphasis added). Thus, Dindzans does not teach or suggest the use of heterozygous mice, and in fact, it teaches against the use of such mice. This is because the homozygosity that is a hallmark of RI lines is that which makes them “useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control”. Accordingly, applicants respectfully submit that Diehl and Dindzans cannot be combined to teach or

suggest employing individuals that are heterozygous for a detectable polymorphism for genetic mapping because each teaches that mice that are homozygous at every locus are required in order to perform genetic mapping. Applicants respectfully submit that herein lies at least one aspect of the non-obviousness of the instant application, which teaches genetic mapping of renewable populations of genetically diverse individuals.

Additionally, it is noted that while both Diehl and Dindzans might employ populations that have different alleles at various loci, the instant claims require that individuals have different alleles at various loci (*i.e.*, that are genetically diverse). Applicants respectfully submit that Diehl and Dindzans actually teach against employing individuals that are genetically diverse.

Applicants further respectfully submit that Hedrich does not cure this deficiency of the combined references. The Patent Office asserts on page 14 of the Official Action that "Hedrich's teaching of 8-10 breeding pairs makes obvious the use of at least 3, 4, or 8 non-recombinant parent lines of Dindzans...". Applicants respectfully submit that the Patent Office offers no support for this contention. Applicants reiterate that there is no correlation between Hedrich's teaching of multiple breeding pairs and Dindzans non-recombinant parent lines, and that one of ordinary skill in the art would not have read Hedrich to suggest using 3, 4, or 8 different non-recombinant inbred lines to establish an RI line.

Rather, applicants respectfully submit that at best one of ordinary skill in the art might interpret Hedrich to teach that multiple mating pairs can be beneficial in maintaining each recombinant inbred line since not all mice will reproduce. However, it is noted that for each RI line, the members of the multiple mating pairs will be genetically identical, and thus are not genetically diverse as that phrase is defined in the instant specification.

Furthermore, applicants respectfully submit that there are no references cited by the Patent Office that employ more than two non-recombinant inbred lines. Applicants respectfully submit that both Diehl and Dindzans employ only two non-recombinant parent lines. In Diehl, the mice are recombinant (*i.e.*, NOT non-recombinant) inbred lines derived from AXB and BXA, which one of ordinary skill in the art knows are

generated from A/J and C57BL/6 crosses. Thus, Diehl teaches exactly two non-recombinant inbred lines: A/J and C57BL/6. In Dindzans, the exact same two non-recombinant inbred lines are employed. Thus, Dindzans also does not teach 3, 4, or 8 non-recombinant inbred lines.

With respect to Hedrich, the entire reference is concerned with the maintenance and propagation of a single non-recombinant inbred line. To elaborate, applicants respectfully submit that the citations from the Hedrich reference that have been relied on by the Patent Office are from a section of Hedrich entitled "Inbred Strains". As is known in the art, inbred strains are strains that are homozygous at every locus. Thus, applicants respectfully submit that the entire Hedrich reference is about generating and maintaining an inbred line, and more particularly is concerned with ensuring that the line maintains its homozygosity at every locus and is not lost by maintaining too few individual that may not reproduce.

This is clearly disclosed on page 170 of Hedrich, which states *inter alia* the following:

- laboratory animal populations are genetically unstable;
- strains and substrains deviate in their genotypic structure from the original genetic pattern;
- deviant alleles (foreign or new) must be detected, and if possible eliminated, in inbred strains before they are fixed in the homozygous state.

Thus, Hedrich teaches the propagation of a non-recombinant inbred strain and ensuring the genetic identity of its members both with other members of the strain and with the original members of the strain.

According to Hedrich, this is accomplished by organizing breeding colonies and testing these breeding colonies for the presence of "deviant alleles". On page 171 under the heading "**2. Organization of the Breeding Colonies**", Hedrich states that "the propagation of an inbred strain is divided into three groups: foundation colony (FC), pedigreed expansion colony (PEC), and production colony (PC)" (emphasis added). Thus, Hedrich discloses breedings designed to maintain an inbred strain.

Furthermore, applicants respectfully submit that all members of the FC, PEC, and PC are members of the same inbred strain. The reference in Hedrich to “selecting among the lines that one which matches the original standards best” is thus not suggestive of introducing heterozygosity, but eliminating it. Applicants respectfully submit that “original standards” refers to the homozygous “genetic profile” that the original inbred strain has (or had). Thus, even the disclosure of “8-10 breeding pairs” in Hedrich does not suggest using 3, 4, or 8 different non-recombinant parent lines to create individuals that are heterozygous for a detectable polymorphism as recited in claim 1 because the entire purpose of the breeding pairs of Hedrich is to maintain mice that are homozygous at every locus by eliminating any deviant alleles (i.e. to eliminate polymorphisms). Thus, applicants respectfully submit that the disclosure of Hedrich also teaches against using individuals that are heterozygous for a detectable polymorphism.

Summarily, applicants respectfully submit that the Patent Office has not provided any reference(s) that teaches or suggests mapping using renewable populations of genetically diverse individuals, wherein some or all of the genetically diverse individuals are heterozygous for a detectable polymorphism. Applicants respectfully submit that Diehl, Dindzans, and Hedrich teach strategies that depend on homozygosity (Diehl and Dindzans) or are designed to maintain or establish homozygosity (Hedrich), and thus each reference teaches away from introducing heterozygosity.

Applicants respectfully submit that the claims recite using a mapping population made up of individuals each of which is heterozygous for at least one detectable polymorphism. It is axiomatic that in order to establish a *prima facie* case of obviousness, the Patent Office must demonstrate that one of skill in the art would have been motivated to combine Diehl, Dindzans, and Hedrich, and that in doing so, one of ordinary skill in the art would have arrived at the claimed invention. Since Diehl, Dindzans, and Hedrich all teach against using heterozygous animals, applicants respectfully submit that the cited combination cannot be relied on for establishing *prima facie* obviousness under the requirements of M.P.E.P. §§ 2143.01 and 2145.

Accordingly, applicants respectfully submit that the combination of Diehl, Dindzans, and Hedrich does not support a rejection of claims 11-14 and 16-18 under § 103. Thus, applicants respectfully request that the rejection be withdrawn at this time.

Turning now to claims 64-73, applicants respectfully submit that the combination of Diehl, Dindzans, and Hedrich does not disclose or suggest performing a mapping method using animal cell lines that display a phenotype as recited in claim 64, and thus the combination of Diehl, Dindzans, and Hedrich does not support a rejection of claim 64 under 35 U.S.C. § 103(a). Applicants respectfully submit that the Patent Office has provided no rationale for why one of ordinary skill in the art would have read Diehl, Dindzans, and Hedrich to suggest the subject matter of claim 64. Claims 65-73 all depend from claim 64, and thus are also believed to be distinguished from the combination of Diehl, Dindzans, and Hedrich.

Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of any of claims 11-14, 16-18, and 64-73. Applicants further respectfully submit that these claims are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V.B. Response to the Rejection over Lipp in view of the '438 Patent

Claims 1-10, 15, 19-27, 46-53, and 60-75 have been rejected under 35 U.S.C. § 103(a) over the combination of Lipp and the '438 Patent. According to the Patent Office, Lipp teach a method for identifying a genetic locus that modulates a phenotype and a method for identifying an interaction between a genetic locus and a non-genetic factor, wherein the interaction modulates a phenotype. These assertions are made with respect to claims 1, 3, 4, 19-27, 46, 48-53, 60, 74, and 75. The Patent Office concedes that Lipp do not teach a method wherein the renewable population of plants are produced by backcrossing RI lines comprising less than about 500 lines and further wherein the RI lines are derived from at least 3, 4, or 8 different non-recombinant parent lines. However, the Patent Office asserts that these deficiencies are cured by the '438 Patent, which is asserted to teach the limitations included in claims 2, 8, 9, 11-13, 15-18, 47, and 61-63.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the Patent Office has not provided any arguments as to how the recited combination applies to claims 64 and dependents thereof. Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of claims 64-73, and thus request that the rejection as applied to claims 64-73 be withdrawn at this time.

On page 14 of the Official Action the Patent Office appears to assert that each different soy bean or maize plant is a genetically diverse individual, and that together they can make up a renewable population, and that the genetically diverse individuals are heterozygous for a detectable polymorphism. The Patent Office further asserts that PCR detection of 2 genetic elements corresponds to mapping the genomes, and that detection of the 35S promoter and the NOS terminator satisfy the "identifying a genetic locus" step of claim 1.

First, it is not clear that the soy bean or maize plants correspond to genetically diverse individuals. There is no teaching in the reference that these plants are heterozygous for any detectable polymorphisms. The Patent Office simply assumes this to be true but offers no supporting evidence.

Nonetheless, even assuming *arguendo* that the soy bean and maize plants disclosed were genetically diverse individuals, the Patent Office has also not presented any reasoning as to how these plants can be used to generate a renewable population of genetically diverse individuals. For the reasons set forth in more detail hereinabove, breeding of soy beans or maize plants cannot create a renewable population of genetically diverse individuals unless the parental plants are homozygous at every locus and these homozygous lines are crossed to generate renewable genetically diverse individuals. There is no disclosure in Lipp that any of the plants examined were inbred plants, and thus there is no disclosure in Lipp that any renewable populations of genetically diverse individuals were produced.

In fact, these two possibilities are mutually exclusive. On the one hand, if the individual plants are genetically diverse themselves, they cannot be used to generate a

renewable population of genetically diverse individuals because as described hereinabove, recombination would rearrange the genetic information, rendering each progeny genome unique and non-regenerable. On the other hand, if the individual plants were capable of producing a renewable population, that would mean that they themselves were not genetically diverse because only non-genetically diverse organisms can be bred to produce a renewable population of genetically diverse individuals. Therefore, step (a) of independent claims 1, 46, 60, 64, 74, and 75 is not disclosed or suggested by Lipp.

Furthermore, independent claims 1, 46, 60, 64, 74, and 75 each include a mapping step. Applicants respectfully submit that mapping is defined in the specification as “a method for describing a position of a genetic locus in terms of recombination frequency with a genetic polymorphism” (see page 14). PCR detection of 2 genetic elements does not satisfy this definition because there is no discussion of where on any chromosome any of the 35S promoters or NOS terminators are in any of the plants. Additionally, applicants respectfully submit that one of ordinary skill in the art of genetics would never equate “mapping” merely with “detecting the presence of”. All the PCR protocol in Lipp does is detect whether or not a 35S promoter and/or a NOS terminator is present within a plant. Thus, this step of the methods of independent claims 1, 46, 60, 64, 74, and 75 is not disclosed or suggested by Lipp.

Furthermore, since no mapping step is performed, no loci are identified that modulate a phenotype through the mapping step as recited in claims 1, 46, 60, 64, 74, and 75. Thus, Lipp does not disclose or suggest this step.

Summarily, applicants respectfully submit that Lipp does not disclose or suggest renewable populations of genetically diverse individuals, mapping the genomes of these individuals, or identifying loci that modulate a phenotype through the mapping step. Accordingly, Lipp does not support the instant rejection of claims 1-10, 15, 19-27, 46-53, and 60-75.

The following additional assertions by the Patent Office with respect to Lipp are traversed as being based on an interpretation of the claims that is inconsistent with the specification:

1. There is no teaching in Lipp of mapping analysis of genetic polymorphisms segregating in the renewable populations. There is in fact no teaching of mapping at all, since PCR detection is not a mapping step.

2. Even if insecticidal resistance is a phenotype, the locus that modulates this phenotype in the Roundup-Ready® soy beans or the BT-176 maize is never mapped in any plant in Lipp. Rather, a 35S promoter or a NOS terminator is detected, but the chromosomal location for any of these is not disclosed. Thus, no mapping is performed.

3. The non-genetic factors recited on page 15 are not ones that modulate any phenotype. If the phenotype is insecticide resistance, environmental influences, herbicide use, the amount and type of larvae present, and the presence of non-target insect and animals do not modulate the phenotype of whether or not the plant is resistant to insects that the transgenes, whatever they might be, would afford protection to. Additionally, the Patent Office's statement that these effects "could" all modulate the phenotype of the BT-176 maize plant indicates that the term "phenotype" is being employed in one instance as relating to insecticide resistance, and in the second instance as relating to some other visible trait (overall appearance, perhaps?). In any case, it is clear that if the plant contains the transgene, it will have a specific phenotype caused by the transgene (insect resistance) irrespective of these other purported non-genetic factors.

4. The 35S promoter and the NOS terminator are not genetic loci (see Official Action at page 16). These are nucleic acid sequences, but the term "locus" is understood by one of ordinary skill in the art of genetics to refer to a position on a chromosome that can be mapped (e.g., a specific site for a specific gene on a specific chromosome). Thus, the Patent Office's assertion here is inconsistent with the understanding of one of ordinary skill in the art.

5. The presence of insects is not an interaction that modulates a phenotype (ability to act as an insecticide) because the transgene, whatever it may be, has the ability to act as an insecticide whether or not the insects are present (see Official Action at page 16).



Turning now to the Patent Office's characterization of the '438 Patent, the Patent Office asserts that the '438 Patent teaches the limitations found in claims 2, 8, 9, 11-13, 15-18, 47, and 61-63 with respect to producing a renewable population of plants by backcrossing RI lines comprising less than about 500 lines and further wherein the RI lines are derived from at least 3, 4, and 8 different non-recombinant parent lines. For example, the Patent Office asserts that the '438 Patent teaches crossing plants of an inbred corn line with plants having a different genotype, and hybrid corn plants produced by growing such hybrid maize seeds at column 4, lines 44-48. The Patent Office also asserts that the '438 Patent teaches that more than 8 RI lines can be crossed to provide new hybrid seeds at column 4, lines 31-35.

Applicants respectfully submit that the cited passages do not support the instant rejection of claims 1-10, 15, 19-27, 46-53, and 60-75. First, even assuming *arguendo* that the '438 Patent teaches crossing different RI lines of corn, there is no suggestion in the '438 Patent that these lines can or should be used to map new loci. Thus, it is a hindsight reconstruction to assert that these lines can be employed for that purpose.

Moreover, the ability to perform the crosses does not imply that one of ordinary skill in the art would have been motivated to perform the crosses and then to employ the progeny of the crosses in a genetic mapping protocol. This motivation cannot be found in the '438 Patent, which does not relate to methods for genetic mapping whatsoever. Thus, applicants respectfully submit that the '438 Patent cannot be interpreted to motivate one of ordinary skill in the art to employ the progeny of crossing inbred corn for mapping genes.

Furthermore, the Patent Office appears to assume that the '438 Patent would have motivated the skilled artisan to produce a population of several different such crosses for mapping purposes. This is not disclosed or suggested in the '438 Patent, which merely discloses that new hybrid seeds can be produced by crossing inbred lines.

And finally, the Patent Office's reliance on column 4, lines 31-35 for the proposition that the RI lines can be derived from at least 8 different non-recombinant parental lines is misplaced. While it is true that the '438 Patent discloses 15 different inbred corn lines, there is no disclosure in the '438 Patent that would motivate one of

ordinary skill in the art to produce different RI lines each of which has a genetic contribution in it from 3, 4, or 8 of these lines. Stated another way, even assuming *arguendo* that one of ordinary skill in the art might have been motivated to create a series of corn lines that were derived from pairwise crosses of all of the various lines (*i.e.*, 8 lines paired resulting in 28 different pairs), this does not imply that one of ordinary skill in the art would have been motivated to:

- (a) create RI lines from the progeny of these crosses;
- (b) cross 3, 4, or 8 of these to produce new lines that have genetic contributions from 3, 4, or 8 different inbred lines; and/or
- (c) take the progeny of step (b) and create RI lines from them.

As such, applicants respectfully submit that even if the '438 Patent suggests crosses of these lines, it does not suggest using the progeny for mapping experiments, creating complex crosses of 3, 4, or 8 different inbred lines, producing RI lines from the progeny of these complex crosses, or crossing the resulting RI lines for use in mapping experiments.

Therefore, the Patent Office has failed to establish a *prima facie* case of obviousness of claims 1-10, 15, 19-27, 46-53, and 60-75 over Lipp in view of the '438 Patent because (1) the method of Lipp is a detection method, not a mapping method, and the '438 Patent does not cure this deficiency; (2) the method of Lipp does not identify any genetic loci, it merely detects whether or not two previously identified genetic elements are present, and the '438 Patent does not cure this deficiency; (3) neither Lipp nor the '438 Patent discloses or suggests using any renewable populations of genetic diverse individuals for identifying genetic loci, and thus the combination cannot be read to suggest using renewable populations of genetically diverse individuals for this purpose; and (4) Lipp does not disclose or suggest the creation of RI lines from 3, 4, or 8 non-recombinant inbred parental strains, and the disclosure in the '438 Patent of 15 different inbred corn strains does not cure this deficiency.

Accordingly, applicants respectfully submit that the combination of Lipp and the '438 Patent does not support a rejection of claims 1-10, 15, 19-27, 46-53, and 60-75

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under 35 U.S.C. § 103(a). Applicants respectfully request that the instant rejection be withdrawn, and that the claims be allowed at this time.

### CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.


### DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 07/10/2006

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